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A Multi-Layer Perceptron Network-Based Model for Classifying Stages of Alzheimer's Disease Using Clinical Data

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ABSTRACT

Alzheimer's Disease is a neurodegenerative disorder that progressively impairs individuals' ability to perform daily activities. This irreversible condition cannot be halted once initiated, but early detection may allow for treatments to slow its progression. In this study, clinical data from the Alzheimer's Disease Neuroimaging Initiative dataset were utilized to identify different stages of Alzheimer's and predict the time required for conversion from mild cognitive impairment (MCI) to Alzheimer's Disease. Clinical indicators of Alzheimer's include age, education level, disease progression rate, and cognitive information. Machine learning techniques such as multi-layer perceptron networks, random forests, support vector machines, and decision tree classifiers were employed for binary and multi-class classification of Alzheimer's Disease (AD), Late Mild Cognitive Impairment (LMCI), Early Mild Cognitive Impairment (EMCI), and Cognitive Control (CN). Among these techniques, the multi-layer perceptron network demonstrated superior performance, achieving accuracies of 99.97% for AD vs LMCI, 99.57% for AD vs EMCI, 99.96% for AD vs CN, 95.05% for EMCI vs CN and LMCI vs CN, 99.97% for AD vs LMCI vs CN, 91.2% for EMCI vs LMCI vs AD, 86.25% for CN vs EMCI vs LMCI, 91.94% for CN vs LMCI vs AD, 85.14% for CN vs EMCI vs AD, and 77.5% for AD vs LMCI vs EMCI vs CN. The proposed model has the potential to facilitate early detection and prediction of Alzheimer's stages without the need for imaging scans, thus offering a valuable tool for clinical practice.

1. INTRODUCTION

There is presently no quick, cost-effective method for routinely screening people of the age 65 years and older for Alzheimer's Disease (AD), the most prevalent type of neurodegenerative dementia. AD or dementia prevalence approximately doubles every 5 years in individuals aged 65 to 85 years, from approximately 1% to 2% at 65 years, to more than 30% to 50% by age 85 years [1]. AD takes a critical cost to patients' day-to-day routines, causing a moderate decrease in their intellectual capacities, including memory, language, conduct, and critical thinking. The main causes of AD are plaques and tangles a kind of protein that degenerate neurons in the brain, making individuals lose their memory and become incapable in carrying out their day-to-day activities independently. AD occurs in three stages. At the first phase of AD, brain nerve cells start to degenerate. At this stage an individual doesn't encounter any recognizable symptoms, hence it is extremely challenging to differentiate from normal [2, 3]. To evaluate the AD properly, physiological examination, psychological examination, cognitive examination, and mini-mental state examinations are required [4]. Unfortunately, as of now, there is no treatment for AD [5, 6] and very recently a team of Bengaluru scientists discovered the small molecule TGR63 that can avoid the mechanism that results in neurons dysfunctional in Alzheimer's Disease [7]. Since early AD affected individuals have different symptoms, it is difficult to identify treatment for AD at its early stage [8]. For this reason, researchers started to use current medical data of individuals to recognize AD at their earliest stages. Very recently, two AD clinical trials have stopped their drugs as they failed to prevent the progression of AD. One of the risk factors for AD is the formation of plaques and tangles in different regions of the brain, which causes physical changes to the brain. These changes also help to check the progression of AD. For example, neurons in the hippocampus that started to decline was one of the earliest changes noticed in AD individuals. The AD progression speeds up the decay of brain tissues and it is proven by increased enlargement of brain ventricles. Moon et al. [9] shows that brain ventricles of AD individual expand four times faster than the normal individual. Although there is no remedy for AD, analysts are striving to find novel treatment techniques that may help slow or stop the disease. These medicines are bound to help the patients in the beginning phase of the illness before they have experienced serious cell harm. The utilization of perceived biomarkers, those dependent on amyloid-beta in the CSF and sub-atomic imaging of cerebrum amyloid affidavit utilizing positron

outflow tomography, is encouraged to help early determination [10, 11]. The early stage of AD can be also diagnosed by cognitive test like ADAS11 and ADAS13 [12], that are based on the Alzheimer's Disease Assessment Scale (ADAS). The ADAS was developed in 1980 to find out the level of cognitive dysfunctions in AD. ADAS11 includes 11 tasks related to observation assessment. Based on the response of the individual a score is assigned that range from 0 to 70, and ADAS13 includes 13 questionnaires related to subject completed test, give the scores lies between 0 and 85, in that least score indicates there is no complication in cognitive level of individual and highest score value denotes individual are at advanced stage of AD [13]. Progression of AD can also be track by other cognitive test like Mini-Mental State Examination (MMSE) [14], the Rey Auditory Verbal Learning Test (RAVLT) [15], Geriatric Depression Scale [15] and the Functional Activities Questionnaire (FAQ) [16]. The paper is systematized as follows; section 1 describes the features, progression symptoms, and causes of AD. In section 2, the state-of-the-art existing methods are reviewed. In section 3 discussion about material and method is done. The section 4 summarizes the method used. The results are discussed in section 5 and in section 6 the conclusion is given.

2. RELATED WORK

While modern clinical, neuroimaging, and cerebrospinal fluid studies are highly accurate in diagnosing Alzheimer's Disease, they are prohibitively expensive for large-scale screening. Furthermore, these technology and specialized services are not readily available to everyone, such as rural seniors and ethnic minorities, limiting their usage as AD screeners. Clinical data, on the other hand, would give a speedy and cost-effective way of screening for AD at the population level, therefore expanding worldwide access to care. Recently machine learning techniques and deep learning methods shows a great success in detection of AD. For example, Ricci et al. [15] have used both MRI and clinical data that considered 3 features like Functional activities questionnaire (FAQ), Neuropsychiatric Inventory (NPI), and Geriatric depression scale (GDS) for diagnosing Alzheimer's at its early stage using SVM, Ensemble, K nearest neighbour and decision tree and achieved an accuracy of 98.4% for the Alzheimer's vs normal and achieved 79.8% of accuracy for AD vs Normal vs MCI.

Altaf et al. [16] used clinical data collected from the ADNI dataset consisting of 8 features like Montreal Cognitive Assessment, Clinical Dementia Rating, Neuropsychiatric inventory questionnaire, Neuropsychological information, Mini-Mental State Examination, Geriatric depression scale, Everyday cognition, and Functional assessment questionnaire for learning the progression of AD as low, medium and high using machine learning techniques and achieved an accuracy of 84.54.

Albright [17] has conducted an experiment to predict the duration for the conversion of normal to AD by utilizing clinical data received from ADNI in which they choose 14 features and generated one additional feature such as month duration. They have applied machine learning models like multilayer neural network, recurrent neural network, and other machine learning algorithms, in that multilayer neural network, a recurrent neural network works well with mAUC 0.866. The authors evaluated the models using a 7 fold cross-validation method.

Eke et al. [18] utilized a blood plasma dataset downloaded from the ADNI website to detect Alzheimer's at its early stage by applying a support vector machine [SVM] and achieved the sensitivity of 80%, specificity of 70%, and area under the receiver operating curve (AUC) of 0.80. For model evaluation, Eke et al. [18] has considered 10 fold cross-validation.

3. MATERIAL AND METHOD

3.1 Dataset

In this experiment consider the clinical study data downloaded from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). The dataset consists of 352 Alzheimer's Disease (AD) samples (192 male, 160 Female), 625 Late mild Mild cognitive impairment (LMCI) samples (382 male, 243 female), 316 (174 male, 142 female) are Early Mild cognitive impairment (EMCI) and 450 CN samples (231 male, 219 female). Each category of a disease considered 16 features and are described in Table 1. These 16 features include basic patient details like AGE, PTGender (patient gender) and PTEDUCA (patient education), genetic feature APOE4, the cognitive test features like MMSE, FDG, ADSA11, ADAS13, 4 types of RAVLT scores, FAQ (Functional Assessment Questionnaire) score, physiological measurement features such as ventricle and hippocampus volume. The correlation between few features is represented by pair lot graph and is shown in Figure 1. In addition to these 16 features, 2 more features are added that are obtained from the data preprocessing steps such as earlier diagnosis results (like control, MCI, or AD) and clinical examination duration.

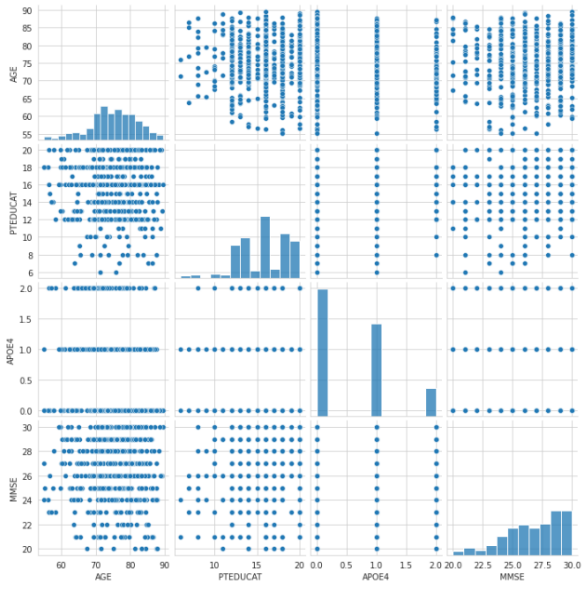

Figure 1. Pair plot graph

3.2 Multi-layer perceptron network

Since there is an accuracy drop in existing methods used by several authors as seen in literature, the accurate method needs to be developed. In this paper a sincere effort is made to achieve accurate results by using a Multi-layer perceptron network (MLPN). The MLPN is a neural network made up of an input layer, hidden layer, and output layer are connected

through channels. Each channel is assigned with weights. The layers consist of perceptron and are associated with bias. The MLPN follows backpropagation and it iteratively adjusts the weight in the network in order to minimize the cost function. In each iteration gradient of weight and bias are calculated to update the weights of the hidden layer and they are propagated back to the starting point of the multi-layer network. The perceptron in each layer receives the product sum of input and weight values and are added with bias value as shown in Eq. (1).

$$r_i = b_i + \sum_{i=1}^{n} x_i w_i \quad (1)$$

For the resultant value obtained from Eq. (1) activation function is applied as shown in Eq. (2). Since in this work multi class classification is done, the softmax activation function is used.

$$b_i = \sigma(r_i) = \frac{e^{r_i}}{\sum_{k=1}^{m} e^{r_j}} \quad (2)$$

This activation function makes the perceptron trigger and gives the output. The output b_i received from the i^{th}. Perceptron is compared with the expected output y_i and error is computed as shown in Eq. (3).

$$E = \frac{1}{2}\sum_{k} (b_k - y_k)^2 \quad (3)$$

where, b_k is the predicted value and y_k is the expected value. The error from all perceptron is computed and added together to compute the total error as shown in Eq. (4).

$$T_e = E_1 + E_2 + E_3 + - - - + E_n \quad (4)$$

where, T_e is the total error, E_1 is the error of 1st perceptron and E_n is an error of n^{th} perceptron. If the T_e is more than pre-defined error then making the network learn the input values again by adjusting the weight values of a channel in such a way that will reduce the error. So optimizing the network by using adam optimizer, it will update the weight value by calculate the gradient of weight values of each channel as given in Eq. (5).

$$\nabla[W_1 , W_2 W_3 \ldots\ldots W_n] = \begin{bmatrix} \frac{\partial f(x_0, x_1 - - - - x_n)}{\partial x_0} \\ \cdot \\ \cdot \\ \cdot \\ \frac{\partial f(x_0, x_1 - - - - x_n)}{\partial x_n} \end{bmatrix} \quad (5)$$

where, ∇ is the gradient sign and

$$\nabla[W_1] = \frac{\partial f(x_0, x_1 - - - - x_n)}{\partial x_0} = \frac{1}{n}\sum_{i=1}^{n} x_i (b_i - y_i) \quad (6)$$

where, W_1 is the weight of first channel and $\nabla[W_1]$ indicates gradient of W_1 and use this gradient descent to update the value of W_1 and it is given in Eq. (7).

$$W_1 = W_1 - \alpha \nabla[W_1] \quad (7)$$

where, α is the learning rate and the model performance rate is varied with respect to the learning rate.

In same manner gradient of bias value is also calculated and is given in Eq. (8).

$$\nabla[\text{Bias}] = \frac{1}{n}\sum_{i=1}^{n} (b_i - y_i) \quad (8)$$

Use this error gradient to update the bias and is given in Eq. 9.

$$\text{Bias} = \text{Bias} - \alpha \nabla[\text{Bias}] \quad (9)$$

This updated weights and bias feed back to the hidden layers and continue the process. This process is repeated till input values are linearly divided into separate regions.

4. PROPOSED SYSTEM ARCHITECTURE

The proposed system architecture is depicting in Figure 2. The sequences of steps followed are, Loading the Data, Data preprocessing (Data all pairing, data normalization, and data resampling), separate the dataset into train and test data, Build the network model, Training the classifier model by using training data and testing the model by using testing data. The training model will train to predict the probability of the disease and also predict the duration required for the transferring the disease from mild cognitive stage to Alzheimer's. Compare this probability result with test data and finally evaluate the system.

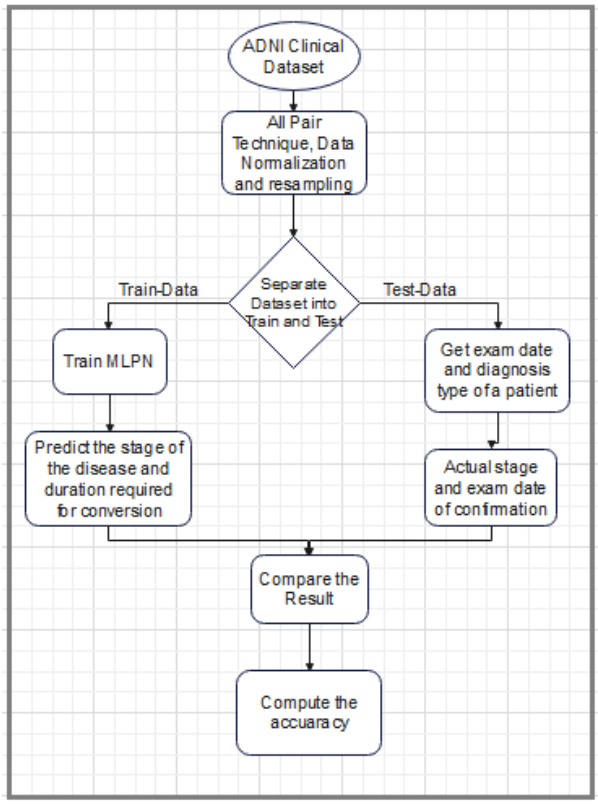

Figure 2. Proposed system architecture

4.1 Data pre-processing

The system performance can be advanced by preprocessing the data. Data pre-processing involves all- pair technique [19],

data normalization and data resampling. The all-pair method is summarized as follows: In ADNI dataset each individual has many clinical records recorded at different months. Let M be the total number of individual and N be the number of biomarkers being used as features. In ADNI dataset every patient A_i ($1 < i < M$), incorporates B_j examinations records. Let, $E_{k,l}$ be the lth examination record of the kth patient, be characterized as follows:

$E_{k,l}$=[$D_{k,l}$,$b_{k,l,1}$, $b_{k,l,2}$,--- $b_{k,l,N}$, $d_{k,l,}$] where $D_{k,l}$ is the date of the examination, $b_{k,l,X}$ (where $1 < X < N$) are various biomarkers , and $d_{k,l,}$ is the patient clinical condition like AD, MCI, CN. By using these clinical examination values generate input vector X and targeted output vector Y are given in Eqs. (10) and (11).

$$X = [D_{k,l_b} - D_{k,l_a}, b_{k,l,1}, b_{k,l,2}, - - - b_{k,l,N}, d_{k,l}] \quad (10)$$

$$Y = d_{k,l_b} \quad (11)$$

The all-pair method is followed by data normalization. The system performance is improved by normalizing the field values, it can have done by applying the Labelencoder function imported from sklearn. Preprocessing library. The Labelencoder function encodes field values between 0 and number_of_classes-1. And also in this step replace all missed values by mean or median values of the respective column. Sample of pre processed dataset is shown in Figure 3.

After Data normalization data resampling is performed. The machine learning technique works well on classification data with an equal number of observations for each class. In case classes consist of an unequal number of observations there is a possibility that the machine can learn non important data and it can omit the important data. So to balance the data sampling comes into the picture. The Synthetic Minority Oversampling Technique (SMOTE) [20] function plays important role in our work. Initially, evaluated the models with an imbalanced dataset and achieved average improvement in accuracy because the machine learning techniques bias towards categories with more data. After that, trained the models with SMOTE function. Each model achieved a 5% of improvement in its accuracy for all possible classifications. The SMOTE method balances the dataset by increasing minority class count by duplicating them without affecting their originality. The SMOTE method will not affect the original dataset instead that it places a virtual replica of the dataset by randomly choosing one among the k-nearest neighbors for each example in the minority class.

	PTGENDER	AGE	PTEDUCAT	ABETA	TAU	PTAU	MMSE	ADAS11	ADAS13	RAVLT.immediate	RAVLT.learning	RAVLT.forgetting	FAQ	Ventricles.bl	Hippocampus.bl
910	0	40	10	266	282	135	12	49	69	36	6	16	4	126	419
337	0	143	10	184	417	155	3	39	62	34	5	15	11	546	400
660	1	188	10	436	35	13	12	6	14	33	12	14	0	586	631
207	0	52	10	173	198	82	10	25	45	34	3	15	3	255	687
444	1	199	6	278	575	366	11	21	41	13	5	7	1	290	485
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
994	1	121	10	307	358	212	11	1	1	62	9	5	1	521	664
262	0	164	4	83	244	112	11	31	51	33	6	4	0	30	624
812	1	293	5	289	412	455	12	18	20	21	4	11	12	494	172
997	0	105	14	556	133	237	3	76	103	9	2	8	0	692	41
429	0	163	7	519	584	228	11	15	17	30	4	9	0	462	785

1106 rows × 15 columns

Figure 3. Preprocessed dataset

4.2 Method

After the data pre-processing, for evaluation purposes, divided the entire dataset into train and test datasets with ratios 70 and 30. Again 10% of the training dataset is considered as validation. This process results in 592 training data, 76 validation data, and 74 subjects for testing data. The model is trained by using training dataset and the test dataset is utilized for evaluating the model. Here trained the machine learning models like Multi-layer perceptron network, random forest, Support vector machine, and decision tree classifier using 10 fold cross-validation method. Among all these machine learning multi perceptron network shows the best performance. Here 10 fold cross-validation is use as a batch size, the dataset D is partitioned into 10 subsets of data d_i where i<=10 and the model is iterated for 10 fold. In each iteration, the model considers 1 fold of data for testing and the remaining 9 fold for training. And also to improve the accuracy we make models to repeat this process for 15 iterations. The box plot accuracy for the multi-layer perceptron network is shown Figure 4, it gives an accuracy of 97% without iteration and gives 98.57% of accuracy after it is trained for 15 iterations. The proposed multi perceptron network is shown in Figure 5. The working flow of proposed method is shown in algorithm below.

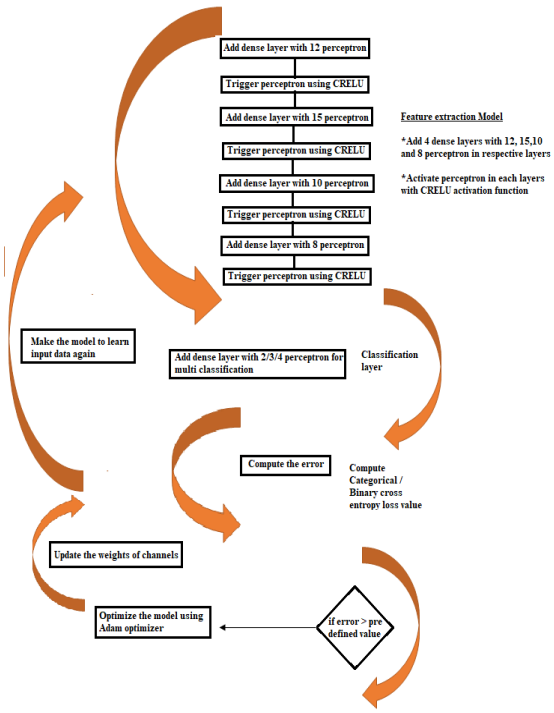

Figure 4. Proposed multiperceptron network

Algorithm:
Step 1: Preprocess the dataset
// Preprocee the dataset by fill null values in the column by mean and median value of that column and also by applying Lineencoder.
Step 2: Balance the dataset by applying SMOTE
Step 3: Divide the dataset into train(D_{train}) and (D_{test}) dataset
Step 4: Train the dataset (D_{train})
Create multi layer perceptron
Model:Add.dense(15)
Add.dense(8)
Add.dense(16)
for i in range(16)://for 15 iteration
for j in range(11)://for 10 fold validation
Divide (D_{train}) into $d_1, d_2, d_3 - - - d_{10}$
$Fold_{test}$ = Model($d_1, d_2, d_3 - - - d_{10}$)
$Fold_{train}$ = $d_1, d_2, d_3 - - - d_{10}$ - $Fold_{test}$
Model.fit($Fold_{train}$)
Model.predict($Fold_{test}$)
Step 5: Model.Evaluate(Accuracy)

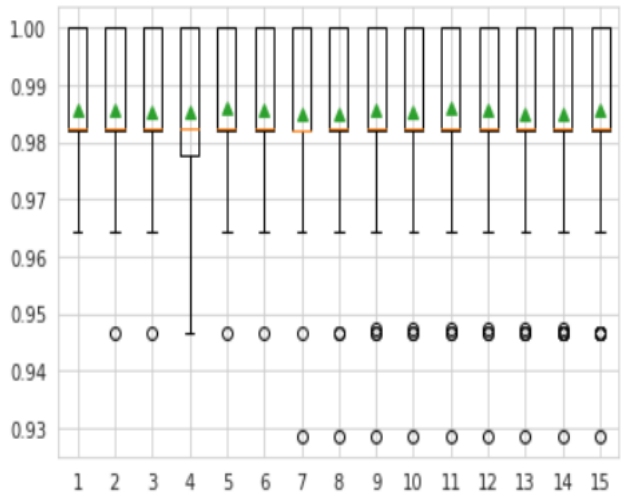

Figure 5. Accuracy box plot of multi-layer perceptron network

5. RESULTS

The Proposed work was implemented using Google Colab. We progressively achieved the results by increasing the epochs using a windows platform system with an i3 Intel processor@1.70GHZ and 4 GB RAM. Performance of the classification system is estimated by measuring sensitivity, specificity, accuracy, and finally plotting the receiver operating characteristics (ROC) curve. The ROC is a useful tool to predict the probability of binary classification and multi-classification outcomes. The ROC is a graph of the false positive rate versus the true positive rate. True positive rate(sensitivity) and false-positive rate are given in the following Eqs. (1) and (2).

$$True\_Positive\_Rate = \frac{True\_positive}{(True\_positive + False\_Negitive)} \quad (12)$$

$$False\_Positive\_Rate(FPR) = \frac{False\_Positives}{(Fals\_Positives + True\_Negitives)} \quad (13)$$

where, True_positive demonstrates number of positive classes accurately classified, False_positive shows various negative classes are named positive, False negatives are various positive classes named negative and True negatives are various negative classes are delegated negative. TPR demonstrates what percentage of the positive classes got accurately characterized and FPR shows what percentage of the negative class got erroneously arranged by the classifier. The larger TPR and the lower FPR is making the model more efficient.

Presently two strategies of ROC AUC are supported, one among them is the one-versus-one algorithm measures average of pairwise ROC AUC score and another strategy is one-versus-rest measures the average of ROC AUC curve score of each class against the rest of the classes. Here use one-versus-rest. The following figure shows the ROC AUC curve for binary and multi-classification. The Y-axis of ROC AUC indicates TPR and X-axis indicates FPR. The top left corner is the peak point where the FPR is close to zero and the TPR is close to one. The Area Under the Curve (AUC) is summarizing the ROC curve and it shows the classifier ability to distinguish the classes. The higher AUC represent that the model shows the best performance in categorizing the positive and negative classes. Figure 6(a) shows the ROC AUC curve for CN vs AD classification, where AUC is 99.9%. Figure 6(b) shows ROC-AUC for CN vs LMCI vs AD and the score is 92%. Figure 6(c) shows the ROC-AUC of CN vs EMCI vs LMCI vs AD and the score is 82%. It shows that the model works well for all binary and trinary classifications of AD, LMCI, EMCI, and CN. But with respect to the 4-way classification, it shows average performance as shown in the figure. The figure depicts that, the ROC-AUC score value of LMCI category is least as compared with other three categories, address that the model shows additional challenges in isolating LMCI people from the other three classes. Totally the model's average performance is 0.89 it could be improved assuming the model capacity is improved to isolate LMCI patients from different classifications.

The confusion matrix of the multi-layer perceptron network is shown in the Figure 7. It shows how well the disease is predicted by the model. The confusion matrix reveals errors for a few cases made by the multilayer perceptron model, like declaring the cognitive normal individual as early/late mild cognitive diseased individual and project normal diagnosis individual as EMCI or LMCI patient. The Figure 8 shows the expected and actual values in the progression of AD for one of the individuals predicted by the model. As there is no well-defined medicine for Alzheimer's projecting the progression of Alzheimer's might help the individual to make decisions about their future.

A Scatter plot of the accuracy of multi-layer perceptron network for binary and multi classification is shown in the Figure 9. The proposed multi perceptron work is compared with other machine learning models like random forest, SVM and decision tree classifier. In that multi perceptron network shows best performance by giving an average accuracy of 91.2% and is shown in Table 1. The accuracy comparison graph for different machine learning models is shown in Figure 10. In Table 1 listed the accuracy obtained by multi-layer perceptron network, random forest classifier, svc, and decision-tree-classifier. Among these Multilayer perceptron network shows the best performance by giving an average accuracy of 91.2%. Here experimented multi perceptron network with various activation functions like RELU, PiSH,

SELU, cRelu and ELU. In that perceptron network shows good performance with cRelu function for both binary and multi classification. A comparison graph of this accuracy is shown in the Figure 11. The accuracy comparison table for different activation function is given Table 2.

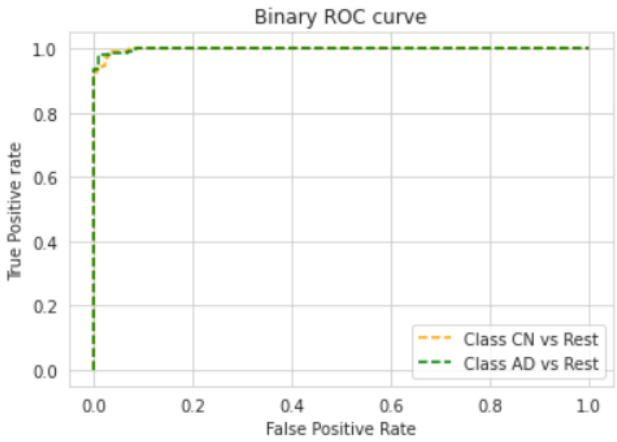

Figure 6(a). Binary ROC-AUC curve

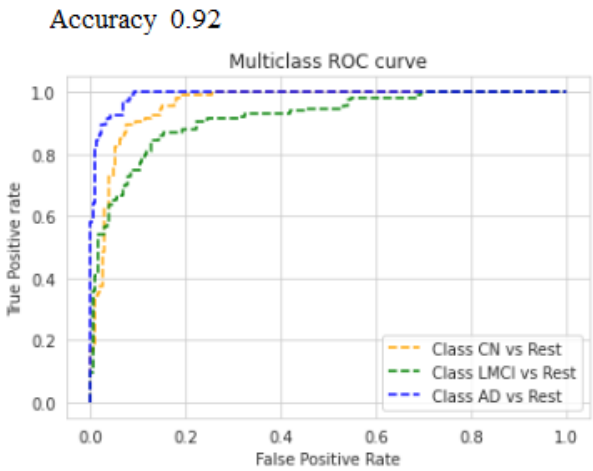

Figure 6(b). Multi class (CN, LMCI and AD) ROC-AUC curve

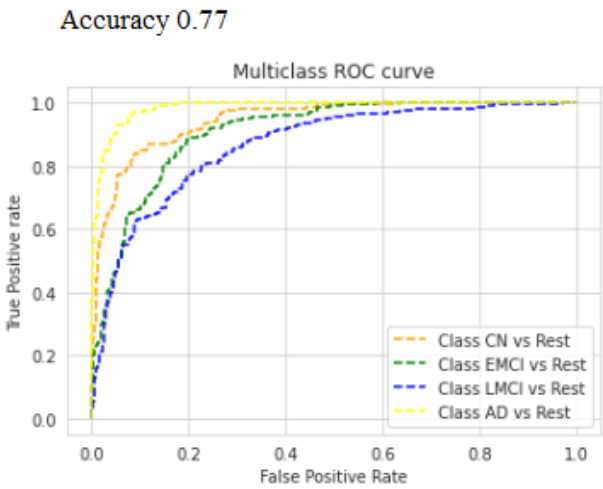

Figure 6(c). Multi class (CN, EMCI, LMCI and AD) ROC-AUC curve

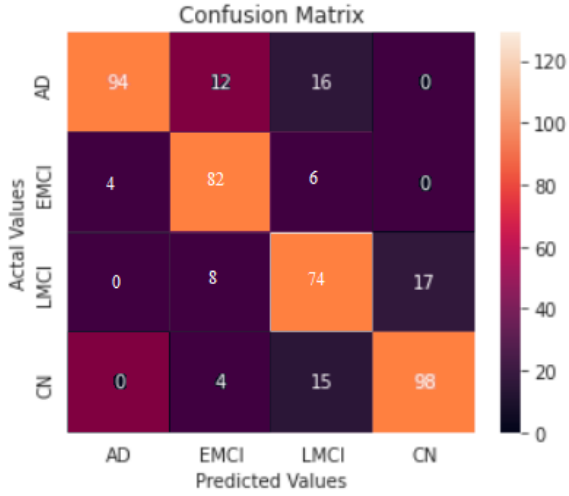

Figure 7. Confusion matrix

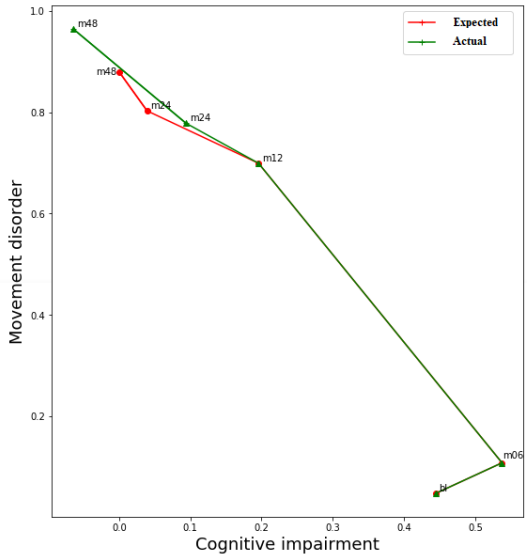

Figure 8. Prediction of movement disorder and cognitive impairment

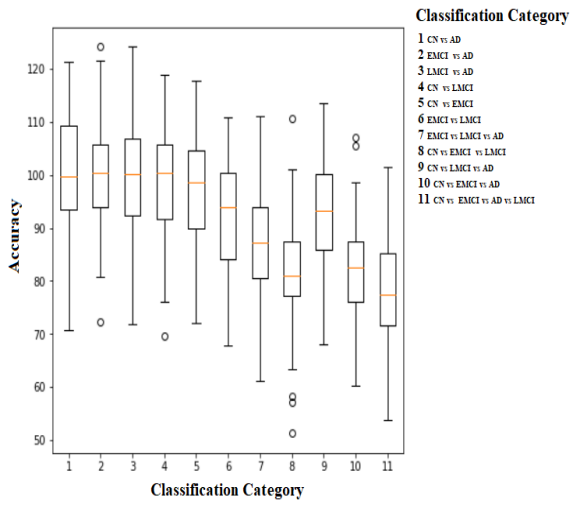

Figure 9. Scatter plot for accuracy of Multi-layer perceptron network

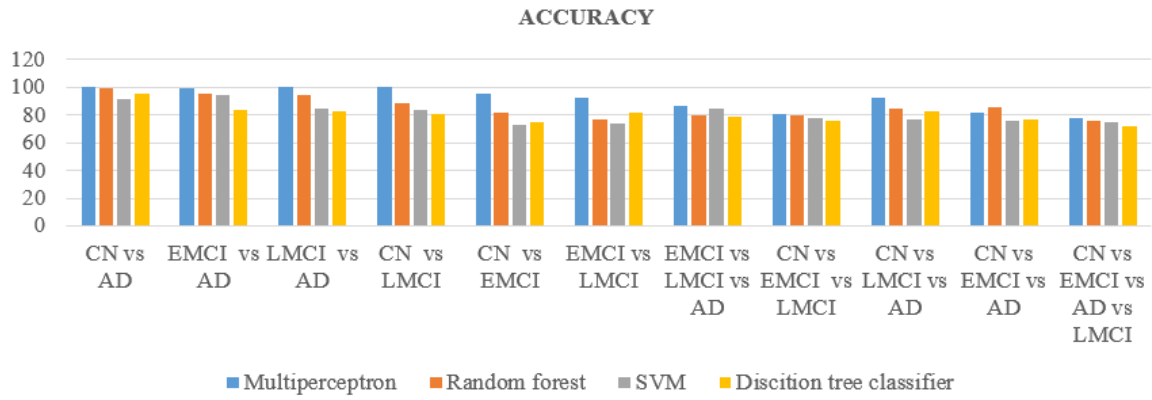

Figure 10. Accuracy comparison graph for different machine learning models

Table 1. Accuracy comparison table for diiferent machine learning models

Classes/ Models	Multi Perceptron Network	Random Forest Classifier	SVC	Decision Tree Classifier
CN vs AD	99.96	98.8	91	95
EMCI vs AD	99.57	95.52	94	84
LMCI vs AD	99.74	94.8	84.3	82.6
CN vs LMCI	99.77	88.8	84	81.1
CN vs EMCI	95.05	81.3	73	75
EMCI vs LMCI	92.74	76.8	74	82
EMCI vs LMCI vs AD	86.25	79.8	84.3	78.5
CN vs EMCI vs LMCI	89.32	80.1	77.3	75.5
CN vs LMCI vs AD	91.94	84.6	77	82.5
CN vs EMCI vs AD	81.21	85.5	76	77.2
CN vs EMCI vs AD vs LMCI	82.76	75.5	81	72

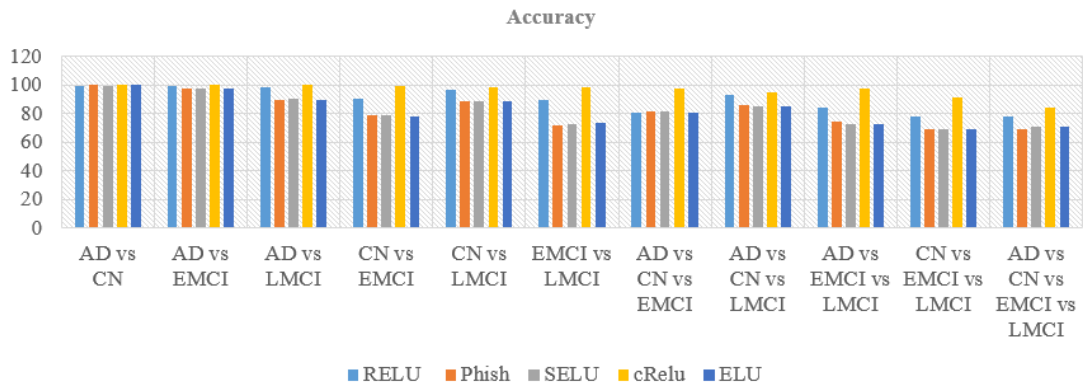

Figure 11. Accuracy comparison graph for different activation function

Table 2. Accuracy comparison table for diiferent activation function

Classes/Activation Functions	RELU	Phish	SELU	cRelu	ELU
AD vs CN	99.74	100	99.74	100	100
AD vs EMCI	99.74	97.66	97.66	100	97.66
AD vs LMCI	98.66	89.93	90.6	100	89.93
CN vs EMCI	90.18	79.22	79	99.09	78.31
CN vs LMCI	96.61	88.61	88.42	98.4	88.82
EMCI vs LMCI	89.6	72.2	73	98	73.4
AD vs CN vs EMCI	80.43	81.43	81.76	97.18	80.93
AD vs CN vs LMCI	92.94	85.59	85.44	94.59	85.44
AD vs EMCI vs LMCI	84.51	74.44	72.78	97.74	72.93
CN vs EMCI vs LMCI	78.19	69.06	69.31	91.25	69.58
AD vs CN vs EMCI vs LMCI	77.6	69.34	70.93	84.62	70.59

6. CONCLUSION

Alzheimer's is a neuron degenerative disease. Currently, no promising medicine is available to treat the AD or to stop the progress of the disease. But detection of dementia at its early stage might help individual families to think about their future regarding financial issues. We put our sincere effort to develop the model using multi perceptron network to diagnose AD diagnosis by using clinical data analysis. Compare to the existing model which works on binary classification, the proposed model shows best performance in multi-class classification. The proposed model gave an average accuracy of 91.2% for binary classification and multi-classification and it also succeed in predicting the probability month of transformation from MCI into AD stage. It shows that the proposed model gives the most promising result. It is considered to be a high-performance model.

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